AUTONOMIC DYSFUNCTION

IN

CHRONIC INFLAMMATORY

DEMYELINATING POLYNEUROPATHY

– A PROSPECTIVE OBSERVATIONAL STUDY

A dissertation submitted in partial fulfillment of Doctor of Medicine- Brach I – Neurology Degree Examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai to be held in August 2014

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ABSTRACT

Title: Autonomic dysfunction in chronic inflammatory demyelinating polyneuropathy

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Objective: To assess the frequency, severity and spectrum of autonomic dysfunction in patients with chronic inflammatory demyelinating polyneuropathy and to correlate autonomic dysfunction with the associated sensory motor deficits.

Methods: Autonomic function was prospectively analyzed in 23 patients meeting CIDP criteria .Autonomic dysfunction was quantified by quantitative autonomic function tests (AFTs) using Finopres. The degree of autonomic dysfunction quantified by using modified CASS. Heart rate variability was assessed using power spectrum analysis. Autonomic symptoms quantified by using COMPASS 31. Severity of neurologic deficits was measured with total neuropathy score (TNS).

Results: Patients mean age was 47.14±13.46 years with duration of illness 4.48±4.30 years. 15 of 23(65%) patients having autonomic symptoms, common symptoms were bowel and sicca symptoms. Autonomic deficits were common (Modified CASS = 3.26 ± 1.91) (19/23; 82%) with moderate severity 11/23(47.8%).Autonomic dysfunction involving both parasympathetic (70%) and sympathetic arms (60%).Spectral analysis of HRV showing abnormality in sympathetic arm. Autonomic deficits did not relate to autonomic symptoms severity, somatic deficits, duration of disease, severity of disease and temporal profile of disease

Conclusion: .There is a high Prevalence of autonomic dysfunction in patients with CIDP(80%). The parasympathetic arm (70%)was more involved than sympathetic(60%).

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a common cause of autoimmune neuropathy, described first in 1958 by James Austin as steroid-responsive relapsing polyneuropathy.(1) In 1975 the disease was characterized at the Mayo Clinic by Prof Peter Dyck and the term CIDP was coined . (2) The prevalence of CIDP from current published data ranges from 1 to 7.7 per 100,000, and increases with advancing age with a peak incidence at 40–60 years of age.(3) CIDP is considered to be a disease with predilection for large myelinated fibers over small myelinated and unmyelinated fibers.(4) In view of the profound motor weakness, emphasis has always been on the motor disabilities and the autonomic dysfunction in these patients' has not been addressed in the Neurology Clinic setting. Both myelinated and unmyeminated fibers are affected in patients with CIDP leading to autonomic dysfunction (5)

Based on previous studies, the prevalence of autonomic deficits in CIDP has been found to be 21% to 76%. (5)(6)(7)

However, most of the studies were retrospective and factors like selection and recall bias could account for the high variability in prevalence of autonomic dysfunction. There is a paucity of Quantitative studies assessing autonomic dysfunction are lacking in both Western and Indian setting. Hence, there is a need for a prospective study to accurately ascertain the actual prevalence of autonomic dysfunction, both clinical and subclinical in a cohort of patients' with CIDP and to quantify the degree of dysfunction. Identifying the domains' of involvement will also help in addressing appropriate treatment strategies.

AIMS AND OBJECTIVES

1. To assess the frequency of occurrence, severity and spectrum of autonomic dysfunction in patients with CIDP

2. To correlate autonomic dysfunction with the associated sensori- motor deficits

REVIEW OF LITERATURE

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common cause of a Chronic Autoimmune neuropathy. Various criteria have been developed to define the disease. Some are stringent criteria and some are based on clinical response, that ensure early recognition and early treatment with immunomodulation/ immunosuppressant drugs.

Despite ongoing clinical challenges with the diagnosis and definition, CIDP can be practically viewed as the chronic spectrum of Guillain–Barré syndrome, owing to similarities in electrophysiological, histolopathological and immunopathogenesis. (8).

CIDP differs from AIDP, by its temporal profile, course of disease and responsiveness to immunosuppressive agents like steroids. (8) Chronic inflammatory demyelinating poly radiculoneuropathy (CIDP) is a heterogeneous disorder. CIDP differs from AIDP as former develops over more than 2 months, where AIDP has an acute onset.(8)

CIDP although is being increasingly recognized and diagnosed clinically, the lack of definitive diagnostic test makes the diagnosis occasionally challenging.

Epidemiology:

Available previous literature showing varied prevalence ranging from 1 to 7.7 per 100,000 and it has high incidence at 4- 6 decade.(3)

The discrepancies in prevalence is linked to several factors, like differences in clinical, electrophysiological criteria and genetic factors .(9)(10) The disease can occur at any age with a mean age of onset being 47.6 years and has a higher prevalence in males than in females.(11) Although a relapsing course seems more common between the second and fourth decade, a chronic non relapsing course is more common between the fifth and the seventh decade.(3)

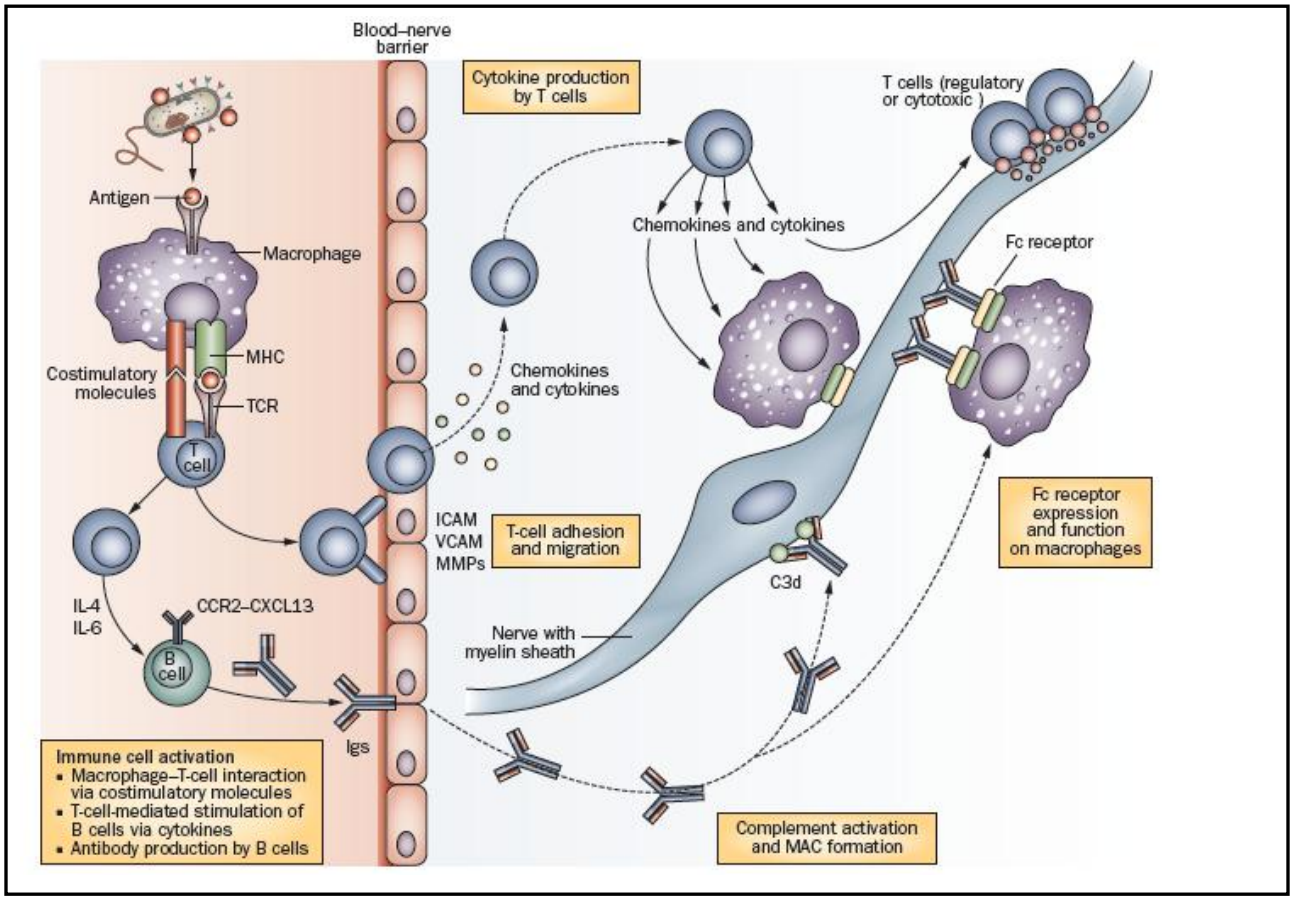
Pathogenesis:

In CIDP, organ specific damage to peripheral nerves due to auto activation of cellular and humoral immunity due to loss of self tolerance(12)

In some individuals immune response to various pathogenic factors leads to break down in self tolerance and results in autoimmune disorders. The inciting factors known to share epitopes with the host's affected tissue.(13)Most commonly various infections were implicated in breakdown of self tolerance.

A high incidence of CIDP in melanoma or patients receiving vaccinations with melanoma lysates due to breakdown in self tolerance.(13)

FIGURE 1: Pathogenesis of CIDP



Cellular immune response

Due to unknown antigens systemic T cells are activated which generate inflammatory lesions in the nerves through blood nerve barrier breakdown by a process which includes homing, adhesion and transmigration. (14)

Levels of soluble adhesion molecules, chemokines, cytokines and matrix metallo-proteinases are increased in the serum, endothelial cells and CSF of patients with CIDP, all of which facilitates lymphoid cell transmigration across the blood–nerve barrier. Derangement of the blood nerve barrier is known to happen due to down regulation of tight junction proteins.(15) Macrophages and Schwann cells present antigen to the CD4+ T cells, through expression of the co-stimulatory molecules CD80 and CD86, which bind to the counter-receptors on the CD4+ T cells i.e., CTLA-4 and CD28.(16)(17) Then T cells undergo clonal expansion thereby activating resident endoneurial or passenger macrophages. Macrophages are the final effector cells that are associated with the demyelinating process. Macrophages release an variety of potentially toxic substances which cause cytotoxic activity against Schwann cells..(18)

Humoral immune response:

Autoantibodies have been implicated in the pathogenesis of chronic inflammatory demyelinating polyneuropathy since more than two decades. This observation was based on c.s.f oligoclonal IgG bands and presence of immunoglobulins and complements on myelinated nerve fibers. .(19) These autoantibodies were implicated in the conduction block and demyelination in experimental models.(20). Recent studies indicate that antibodies to various glycolipids or myelin proteins P0were frequently detected than controls. (20)(21)(22)(23)

Passive transfer of GM1 antibodies from CIDP patients to experimental animals was found to suppress sodium currents in myelinated nerve fibres in experimental animals.(24) Other than myelin- directed antibodies, cytokines, nitric oxide and complements may be involved in the pathogenesis of demyelination and conduction block. Removal of auto antibodies along with toxic substances like cytokines, nitric oxide by plasma exchange has shown to improve prognosis in CIDP. It probably indicates that activated B cells play a role in CIDP.

Target antigens:

Despite detailed investigations the target antigens involved in the pathogenesis of CIDP is yet to be determined. It is postulated that the antigeninc targets may be located within the non-compact myelin and in the points of Schwann cell–axon interaction. Molecules such as neurofascins gliomedin and contactin (contactins-2, CASPR1, connexin, neural cell adhesion molecule, cadherin, ankyrin and others), are the postulated target antigens in human autoimmune neuropathies.(25)(26)

Clinical features:

Acute inflammatory demyelinating neuropathy (AIDP) and CIDP have similar clinical findings, but as the terms imply, the time course is defined by a peak deficit within 4 weeks in AIDP, and after at least 8 weeks in CIDP. Typical cases of CIDP are fairly symmetric, and motor involvement is greater than sensory. Typical CIDP is characterized by a progressive, symmetric, proximal and distal muscle weakness, paresthesias and impaired balance, which evolve slowly over at least 2 months. The course may be slowly progressive or relapsing/remitting.(27) A classic clinical feature is proximal limb weakness, which distinguishes CIDP from the large

group of far more commonly encountered distal polyneuropathies. An important differentiating clinical finding is the discrepancy between the degree of weakness and the absence of atrophy in affected muscles. This finding strongly suggests nerve demyelination, as opposed to axonal loss in which atrophy may be prominent. Tendon reflexes are reduced or absent in all extremities.

Sensory involvement is characterized by numbness, distal paresthesias, poor balance, and impaired proprioception. (28)Sensory involvement is usually greater for vibration and position sense than for pain and temperature, reflecting the involvement of large myelinated fibers. As opposed to the motor involvement, sensory involvement tends to follow a distal to proximal gradient, although finger involvement frequently occurs as early as toe/foot involvement. Cranial nerve involvement is noted in less than 15% of patients. The common nerves involved are facial, bulbar and extra ocular nerves. Vision loss may be present rarely and is because of pseudo-tumour cerebri, which occurs as a result of high protein content in cerebro-spinal fluid. Autonomic dysfunction and ventilatory failure has been reported in less than 10% of cases, much in contrast to GBS. Constipation and urinary retention are seen occasionally but not early into the disease.(29)

Occasionally, patients may present with back pain, lumbar canal stenosis and cauda equina syndrome due to marked nerve root hypertrophy.

Atypical CIDP:

CIDP is a multifocal disease with demyelination affecting spinal roots, plexuses and proximal nerve trunks. (8)(30)The clinical manifestations may hence differ between patients resulting in myriad variation in presentation. Patients with atypical clinical features are grouped within the

broader category of chronic acquired demyelinating polyneuropathy along with CIDP. This group shares similar electrophysiological features, csf findings and response to immmunotherapies.(28)(31)

Atypical CIDP includes pure motor, pure sensory and ataxic patterns, as well as a multifocal pattern in which weakness and sensory loss develop in the distribution of multiple nerves.

The motor variant:

It is a generalized, pure motor demyelinating neuropathy. widespread proximal and distal limb weakness, relative symmetry, no sensory involvement, and response to corticosteroids distinguish it from multifocal motor neuropathy.(32)(33)

The pure sensory syndrome:

It presents with distal sensory loss, but prominent demyelinating motor abnormalities on EMG studies.(34)(35)

Ataxic CIDP variants:

It consists of 2 variants

1) Patients present with sensory ataxia which simulate a sensory ganglionopathy, with absent sensory potentials and normal motor studies. Nerve biopsy may be required to establish the diagnosis.(36)

2) Clinical presentation is similar with sensory ataxia and large fiber sensory loss. However nerve conduction studies are normal. Abnormal somatosensory evoked potentials suggest sensory root involvement. Biopsy of the nerve rootlet similar to that of CIDP and this condition termed as chronic immune sensory polyradiculopathy.(37)

Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM or "Lewis-Sumner Syndrome"):

Clinical presentation is that of a multifocal neuropathy since conduction block is found in affected nerves. However in contrast to multifocal motor neuropathy they also have involvement of sensory nerves and good response to steroids.(38)

A paraparetic form of CIDP:

It is associated with regional leg weakness, sensory loss, striking nerve root hypertrophy, and gadolinium enhancement of the lumbosacral nerve roots on magnetic resonance imaging (MRI) studies.(39)

Distal Acquired Demyelinating Symmetric Neuropathy (DADS):

It simulates a distal sensorimotor neuropathy with demyelinating electrophysiology suggestive of CIDP. DADS may or may not be associated with paraproteinemia. DADS without paraproteinemia predicts good response to therapy similar to typical CIDP, unlike DADS with paraproteinemia. (40)

Laboratory features:

CSF examination, NCS, and nerve biopsy are the key laboratory studies that support a diagnosis of CIDP. Magnetic resonance imaging (MRI) may reveal spinal nerve root enlargement. Serum electrophoresis to detect paraproteinemia is done to exclude a plasma cell dyscrasia.

Nerve conduction studies:

Electrophysiology is a key part of the diagnostic investigation in CIDP. There are currently 17 published sets of electro-diagnostic criteria for acquired demyelinating neuropathies, all requiring some combination of (41)

(1)Reduced conduction velocities,

(2) Prolonged distal motor latencies,

(3) Prolonged F-wave latencies

(4) Conduction block / temporal dispersion

Kelly in 1983 put forth the first criteria to distinguish neuropathies associated with monoclonal proteins as axonal or demyelinating. Albers and Kelly in 1989 revised the initial criteria and specified prolonged distal latency, conduction velocity slowing, prolonged F wave latency, or a temporal dispersion in two or more nerves. A third criteria by AAN was proposed but was found to have a low sensitivity. Thaisetthawatkul and colleagues showed the usefulness of adding dispersion of distal motor action potentials win diagnostic criterion.(42) Currently the EFNS/PNS 2010 criteria seems to be best in identification of patients with CIDP. This criteria includes prolonged distal CMAP duration in one nerve with one or more other demyelinating parameter in another nerve as supportive of definite CIDP, a normal sural with abnormal median or radial SNAP pattern and sensory conduction velocity < 80 % of lower limit of normal (<70 % if SNAP amplitude < 80 % of lower limit of normal) as supportive criteria.(43)

Cerebrospinal fluid analysis:

A lumbar puncture is indicated in most patients suspected of having CIDP. Approximately 90% of patients with CIDP have elevated CSF protein concentrations (> 45 mg /dL). The diagnosis of CIDP cannot be excluded based on a normal CSF protein concentration. In the past elevated protein considered as mandatory. However, protein content can be normal in at least 10% of patients, and the criterion is now considered supportive. The cell count is usually normal, although as many 10% of patients have greater than 5 lymphocytes/mm^3. AAN criteria has suggested that there should be fewer than 10 white blood cells in the spinal fluid, and fewer than 50 cells in patients with HIV infection. Accordingly, the presence of a CSF pleocytosis suggests evaluation for co-infection/ non-infectious granulomatous diseases.

Other laboratory investigations:

Somatosensory evoked potentials are useful in patients with chronic demyelinating neuropathies as root involvement is not accessible to conventional nerve conduction studies.(44)

This technique might be especially useful when assessing for proximal involvement of sensory nerves in patients with normal sural sensory potentials.

MRI of spine with gadolinium sometimes demonstrate nerve root enhancement in some suspected CIDP patients due to breakdown of the blood–nerve barrier at the root level and root hypertrophy at the lumbar or cervical level in patients with CIDP and can rarely cause clinical findings attributable to lumbar or cervical canal stenosis. (45)As inflammation can be widespread along nerves in CIDP, contrast enhancement and hypertrophy are sometimes shown by conventional MRI at the plexus level.

Nerve biopsy:

CIDP is demyelinating disorder involving the spinal roots, plexuses, and nerve trunks in a diffuse manner.

The yield of biopsy in the confirmation in the diagnosis of CIDP was low, due to multifocal nature of disease. Only in 10-15% of biopsy specimens showing inflammatory changes, it was demonstrated in large series of patients in previous studies. Nerve biopsy features were varied from abnormal about 60%(axonal, demyelinating, inflammatory).to normal about 40%(27)

The demyelinating lesions involving proximal nerve leads to distal axonal degeneration resulting in loss of large myelinated fibers. In such cases an axonal type of nerve conduction abnormalities resulting in misdiagnosis as chronic idiopathic axonal polyneuropathy rather than CIDP. In these cases, nerve biopsy might be of value for diagnosis of CIDP.(46)

According to the EFNS/PNS CIDP guidelines, biopsy chosen from the nerve which was affected clinically and electro-physiologically.

The classic pathologic features of CIDP include demyelination, remyelination (onion Bulbs), endoneurial edema, and inflammatory cell infiltrates in the epineurium and endoneurium usually with preferential involvement of the nerve roots. These infiltrates consists of CD81 and CD41 lymphocytes and macrophages within the endoneurium. The perivascular macrophages in clusters in endoneurium suggest the diagnosis of CIDP on nerve biopsy. Analysis of teased fibers is probably the most sensitive method of demonstrating demyelinating changes, which are found in 50% to 80% of nerve biopsy specimens. Nerve biopsy considered in patients having atypical features or poor response to treatment or high suspicion of alternative diagnosis.

Diagnostic criteria of CIDP:

During last 2 decades, there are different published criteria for diagnosis of CIDP and there still is no consensus optimal approach to the diagnosis.

They published criteria includes clinical, laboratory, and electro-diagnostic criteria with definite, probable, and possible categories. The differences between the different criteria related to definition of the clinical profile, electrophysiological criteria for demyelination and requirement for nerve biopsy. The most recent EFNS/PNS 2010 guideline attempts to provide diagnostic criteria for CIDP based on currently available literature plus expert opinion. It contains clinical, electro diagnostic and supportive criteria. The diagnostic criteria are mentioned in the appendix.

CIDP and Autonomic dysfunction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated disorder affecting large myelinated fibers more than small myelinated and unmyelinated fibers. CIDP is characterized predominantly by motor deficits and mild sensory deficits with autonomic nervous system involvement being not well characterized in previous reports. The prevalence of autonomic dysfunction in patients with CIDP varies from 21%-76%. Studies assessing autonomic dysfunction in CIDP patients by quantitative methods are lacking in both western and Indian literature. It is postulated that autonomic dysfunction in CIDP is probably due to demyelination with conduction blocks affecting the vagus nerve and preganglionic sympathetic efferent fibers or small myelinated and unmyelinated afferent fibers. Lyu et al studied cardiovascular autonomic dysfunction and sympathetic skin response in 12 CIDP patients and reported subclinical abnormalities involving both a parasympathetic and sympathetic arms in 25% of patients. SSR abnormality was found in 50% of patients examined.(6)

Yamamoto et al case reports showed dominant autonomic nervous involvement does not exclude a diagnosis of CIDP.(47) Stambolis et al studied autonomic dysfunction in 17 CIDP patients showing a higher frequency autonomic nervous system involvement in CIDP when compared to previous studies. Quantitative autonomic function tests revealed a dysfunction in 76% of patients, involving both parasympathetic and sympathetic arms.(48)

Figueroa et al studied autonomic dysfunction in 47 CIDP patients retrospectively using the CASS, a validated instrument for quantitative autonomic functions. Autonomic symptoms were relatively rare and if present manifest as gastrointestinal and genitourinary complaints. Autonomic deficits were frequent (47%) but very mild and limited to cholinergic arm with sparing of adrenergic arm. There was no correlation of autonomic dysfunction with the duration or severity of the somatic symptoms.(4)(47)Sakakibara et al. studied the micturition disturbances in CIDP patients and found symptoms suggestive of bladder dysfuction in 8 of 32 patients. Urodynamic studies on four symptomatic patients showed disturbed bladder sensation in two, bladder areflexia in one, and neurogenic changes of the external sphincter in one, indicative of peripheral parasympathetic and somatic nerve dysfunctions. Cystometry had shown detrusor overactivity in two patients without any evidence of CNS involvement. (49) Chiang et al. studied epidermal nerve density (END) and thermal thresholds in 18 chronic inflammatory demyelinating polyneuropathy (CIDP) patients. This study showed significantly lower END in patients with autonomic symptoms (4 in 18) than did those without, indicating that epidermal nerve fibers were more depleted in the presence of autonomic impairment.(50)

MATERIALS AND METHODS

Study setting-

The study was conducted in Christian Medical College and Hospital, a 2500 bedded tertiary hospital in South India. It was conducted in the Department of Neurology. Eligible subjects were recruited from the Neurology outpatient clinics or wards.

Study design-

The study design was prospective cross-sectional study.

The study design and methods were approved by the Institutional review board of Christian Medical College, Vellore.

Participants- Inclusion criteria

Patients diagnosed to have CIDP by EFNS/PNS 2010 criteria were included in the study. The criteria are mentioned in appendix.

Patients with peripheral neuropathy seen in the department of Neurology, Christian medical college, Vellore were screened for inclusion in the study with age greater than 18 years fulfilling European Federation of Neurological Societies/Peripheral Nerve Society criteria

Subject enrollment:

If a patient fulfilled criteria for inclusion then they were approached for informed consent. If the patient consented clinical and demographic data was collected the patient underwent a standardized neurological examination.

Total Neuropathy Score was used as a standardized measurement of severity of somatic neuropathic deficits, motor, sensory and autonomic. (65)

The total score is expressed as a composite score ranging from 0 (no impairment) to 40 (maximal impairment). The scoring system is shown in appendix.

COMPASS 31 scoring system was used to score severity of autonomic symptoms. The minimum raw score is zero and Maximum is 75.(66)The scoring system is shown in appendix.

Seven quantitative autonomic function tests (AFTs) were used for assessment: Valsalva ratio, 30/15 ratio, and inspiration– expiration difference for parasympathetic function; and tilt test, handgrip test, beat to beat BP response to Valsalva maneuver and sympathetic skin response for sympathetic function.

Cardiovagal functions tests

i. RR interval variability following deep breathing- the patient sits quietly and then breathes deeply at a rate of 6 breaths per minute. The ratio of the maximum – minimum heart rates to deep breathing is measured.

   Figure 3 showing heart rate variation with deep breathing

ii. RR interval variability on standing (30:15 ratio – the ratio of RR intervals of 30^{th} and 15^{th} beat after standing).

iii. Valsalva ratio (longest phase 4 bradycardia RR interval divided by shortest phase 3 tachycardia RR interval, recorded when performing the Valsalva manoeuvre).

Valsalva maneuver will be performed in supine position; the test will be started after patient is comfortable and relaxed.After 2-3 practice scissions once patient become comfortable with procedure,he is instructed to take a deep breath and blow into the syringe which is connected to a manometer. Patient is asked to maintain a pressure of 40 mm Hg for 15 seconds. Same procedure repeated after 3 minutes, total 3 times and most appropriate maneuver will be selected for evaluation. The following parameters will be measured from maneuver – Figure 4 showing difference stages of Valsalva maneuver

1. Valsalva ratio.

2. Maximum early phase 2 drop in the mean blood pressure

3. Late phase 2 peak mean blood pressure (recovery).

4. Phase 4 mean blood pressure overshoot.

2. Adrenergic functions

i. BP response to tilt/ standing for three minutes (measured at one minute and three minutes- a drop of more than n 20 mm Systolic or 10 mm diastolic is considered abnormal)(2)

After connecting and ensuring proper placement of blood pressure sensor, baseline blood pressure will be measured for 5-10 minutes. Then patient will be tilted up to 70 degree smoothly within 5-10 seconds (ensuring patient safety) .Then blood pressure will be measured every minute. During this period patient will be observed for the presence of any discomfort, chest pain, shortness of breath, dizziness, lightheadedness, and syncope. In case of any sign of an emerging adverse event test will be terminated based on clinical judgment. Duration of the tilt will be at least 10 minutes and continued for 30 minutes if no obvious abnormalities are detected .On completion of test patient will be tilted back to baseline position.

ii. Beat to beat BP response to Valsalva maneuver. (1) BP response to immersion in cold water (a diastolic rise of < 15 mmHg is considered abnormal)

3. SSR (sympathetic skin response)

Standard silver surface electrodes will be used for the recording. They will be placed on sites with maximum eccrine sweat gland density –active electrode on palms and soles,

respectively, reference electrodes on the dorsum of hand and foot, respectively. The response is processed by standard electromyography. Deep inspiration will be used as stimulus to evoke SSR. Presence or absence of wave forms is noted.

Composite score of autonomic dysfunction - CASS will be calculated based on the above data. These tests will help in identifying the domain of autonomic nervous system affected and the site of involvement.). (67). In view of lack of facilities for QSART, SSR was used to assess sudomotor functions. It was incorporated in to CAS scoring and a modified CAS score was used for analysis and it has not been validated yet.

Equipment and data acquisition

The Finometer PRO™ is a noninvasive beat to beat blood pressure measurement and haemodynamic monitoring system that incorporates proprietary Modelflow methodology for cardiac output measurement and other hemodynamic parameters.

The finometer advantage is its accurate and robust continuous measurement in an all-in-one concept. The finometer not only captures the continuous blood pressure waveform, but also automatically computes up to 15 important beat to beat hemodynamic parameters including:

1. Systolic, diastolic and mean arterial pressures

2. Cardiac output.

3. Stroke volume

4. Total peripheral resistance

5. Pulse rate variability

6. Inter-beat interval

7. Baro-reflex sensitivity

The finometer PRO provides accuracy through return to flow calibration using an inflatable arm cuff and direct graphic parameter visualization on a built-in flat screen

Measurement

All AFTs were performed in the laboratory under standardized conditions. All measurements were performed in a silent room with a temperature of 22°–25°C.

Power Spectrum Analysis

PSA was obtained after 15-min rest in a lying position for 5 minutes s and after a 30° head-up tilt for 5 minutes. Data was exported from Finopres machine. CMCdaq version 1.3, a data acquisition, review and analysis soft ware was used to study heart rate variability and to calculate the power spectrum using Fast Fourier Transformation. The spectral components were obtained by harmonic Fourier analysis in the 0.0033–0.5 Hz frequency range, with the power reflecting the square of the amplitudes. LF and HF power were calculated by integrating the spectra over the 0.04–0.15 Hz and 0.15–0.40 Hz ranges. The resulting power was unit less.

Variables

1. Demographic data
2. Total neuropathy score
3. Neurological examination
4. Nerve conduction studies
5. Sympathetic skin response

Study outcome:

Primary outcome was autonomic dysfunction as detected by COMPASS 31 score or autonomic function testing detected by modified CASS score.

Statistical Analysis:

Data entry was done using SPSS software (version 16). Statistical calculations were done using SPSS software. Chi-square test was used to compare categorical variables, and student t test was used for comparison of continuous variables. Odds ratio (OR) and confidence intervals (CI) were calculated. P value of less than 0.05 was considered statistically significant. The Spearman rho tested correlations among continuous variables.

RESULTS

Among the patients attending with peripheral neuropathy to CMC, Vellore, neurology department in last 6 months, 23 patients met clinical and electrophysiological criteria for CIDP.

All patients had negative hematologic, infectious, endocrine, metabolic, rheumatologic, and myeloma screening.

The study population comprised of 87% males and 13% of females.
The mean age at onset of symptoms was 43.04±11.86 years.
The mean age at the time of autonomic testing was 47.14±13.46 years and duration of illness was 4.48±4.30 years.

Among 23 patients temporal profile shows insidious onset and progressive course in 12/23(52%) of patients, 9/23(39%) had remitting and relapsing course and 2/23(9%) had acute onset of CIDP.

At the time of autonomic testing average total neuropathy score was 20.26 ± 4.88 and average COMPASS 31 score was 7.00 ± 4.19.

Among 23 patients, 7 patients were associated with MGUS. In our study 17/18 patients were immunotherapy responsive. Table 1 showing Demographic and disease characteristics of patients with CIDP

Table1: Demographic and disease characteristics of patients with CIDP:

Characteristics	**Values**
Age at onset, years, mean ± SD	43.04±11.86
Male, n/t (%)	20/23(87)
At autonomic testing	
Age, years, mean ± SD	47.14±13.46
Disease duration, years, mean ± SD	4.48±4.30
Acute onset CIDP, n/t (%)	2/23(9)
Progressive course, n/t (%)	12/23(52)
Relapsing and remitting, n/t (%)	9/23(39)
Motor > sensory, n/t (%)	18/23(78)
Immunotherapy responsive, n/t (%)	17/18(94)
CSF	
Nucleated cells (cells/dL), mean ± SD	4.96 ± 5.07
Protein (mg/dL), mean ± SD	117.13 ± 100.97
COMPASS 31 score	7.00 ± 4.19
Total neuropathy score(TNS)	20.26 ± 4.88
CIDP associated with MGUS, n/t (%)	7/23(30)

In our study 18 of 23 had autonomic symptoms, most common symptoms were bowel complaints and sicca symptoms as shown in table to 2.

Table 2: Summary of autonomic symptoms in patients with CIDP:

Symptoms	No. of patients	No. of patients with additional symptoms	Most common additional symptom
Gastrointestinal	12/23	12/12	Sicca symptoms
Genitourinary	5/23	5/5	Sexual dysfunction
Secretomotor (sicca)	15/23	14/15	Gastrointestinal
Orthostatic intolerance	6/23	6/6	Sicca symptoms
Sexual dysfunction	7/23	7/7	Gastrointestinal
Vasomotor (Flushing)	4/23	4/4	Gastrointestinal and sicca symptoms
Sudomotor	11/23	11/11	Sicca symptoms

In our study 19 of 23(82.6%) patients had quantitative autonomic dysfunction.14 of 23(60.9%) patients had sudomotor dysfunction, 18 of 23(78.3%) patients had cardiovagal dysfunction and 18 of 23(68.2%) had adrenergic dysfunction. In our study 8 of 23(34.7%) had mild autonomic dysfunction, 11 of 23(47.8%) had moderate autonomic dysfunction assessed by modified CASS. As shown in tables 3 – 6.

Table 3: Severity of adrenergic score in patients with CIDP:

Adrenergic score	n/t (%)
0	8/23(34.7)
1	4/23(17.3)
2	5/23(17.4)
3	4/23(17.4)
4	2/23(8.7)

Table 4: Severity of cardiovagal dysfunction in patients with CIDP

Cardiovagal score	n/t (%)
0	5/23(21.7)
1	12/23(52.2)
2	6/23(26)
3	0(00

Table 5: Severity of sudomotor dysfunction:

Sudomotor score	n/t (%)
0	9/23(39.2)
1	12/23(52.2)
3	2/23(8.70)

Table 6: Prevalence and Severity of autonomic deficits in patients with CIDP

Autonomic function tests abnormalities	n (%)
Total	19/23 (82.6)
Sudomotor	14/23(60.9)
Cardiovagal	18/23(78.3)
Adrenergic	15/23(65.2)
Modified CASS score, a mean ± SD	
Sudomotor (0–3)	0.61±0.722
Cardiovagal (0–3)	1.09±0.733
Adrenergic (0–4)	1.48±1.47
Total (0–10)	3.26 ± 1.91
Total Modified CASS (1- 3), n (%)	8/23(34.7)
Total Modified CASS (4-6), n (%)	11/23(47.8)
Total Modified CASS (6-10), n (%)	0(0)

Blood pressure changes in Valsalva maneuver showed 4 of 23(17.4%) had 20-40 mmHg fall in blood pressure during early phase 2 and 2 of 23(8.7%) had more than 40 mmHg fall in blood pressure. Blunted late phase 2 response was seen in 13 of 23(56.5%) patients and 7 of 23(30.4%) had absent phase 4 blood pressures over shoot as shown in table 7.

Table 7: Blood pressure changes in Valsalva maneuver in patients with CIDP:

Exaggerated early blood pressure phase 2 fall,	n(%)
≤ 20% mmHg(normal)	19/23(74)
20-40 mm Hg	4/23 (17.40)
≥ 40 mm Hg	2/23(8.70)
Normal late phase 2 response, n/t (%)	10/23(43.50)
Blunted late phase 2 response, n/t (%)	13/23(56.50)
Normal phase 4 blood pressure over shoot, n/t (%)	16/23(69.60)
Absent phase 4 blood pressures over shoot, n/t (%)	7/23(30.4)

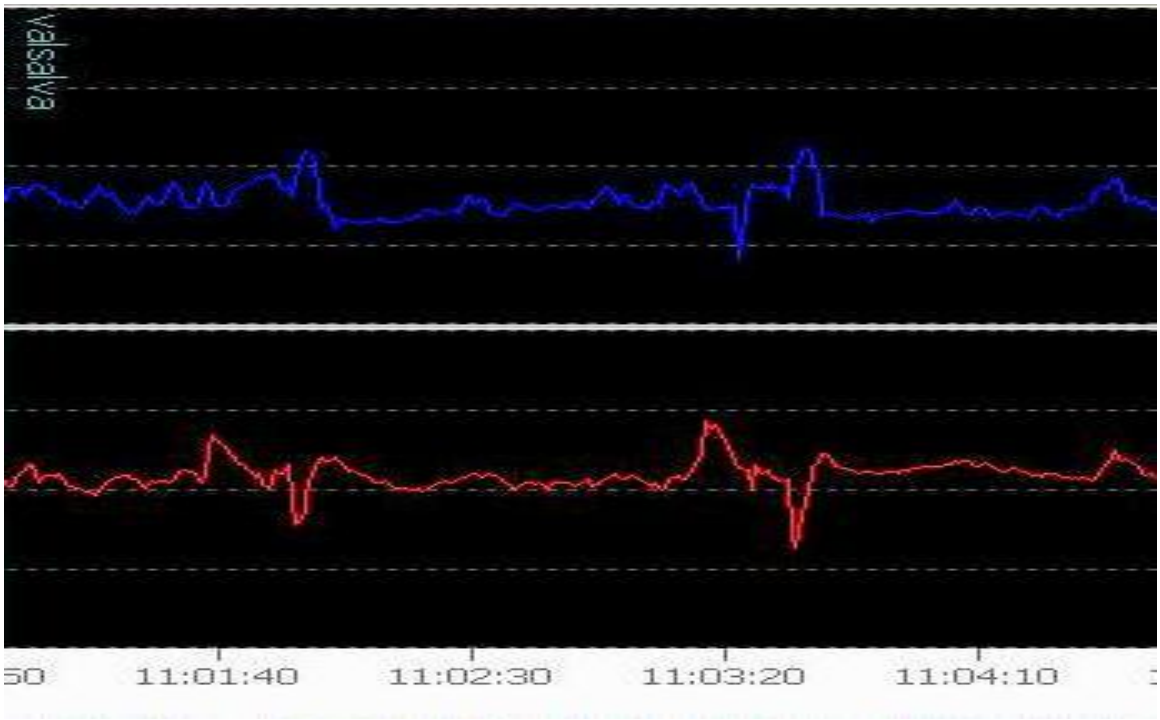


Figure 2: Stages of Valsalva maneuver Red colour indicate blood pressure and blue colour indicate pulse rate. X-axis indicate time and Y- axis indicate pulse rate and blood pressure

5 of 23(21.7%) patients had orthostatic hypotension during head up tilt test and all these were clinically asymptomatic.

Table 8: Abnormalities in head up tilt table test in patients with CIDP

Orthostatic hypotension	n/t (%)
Present	5/23 (21.70)
Absent	18/23(78.30)

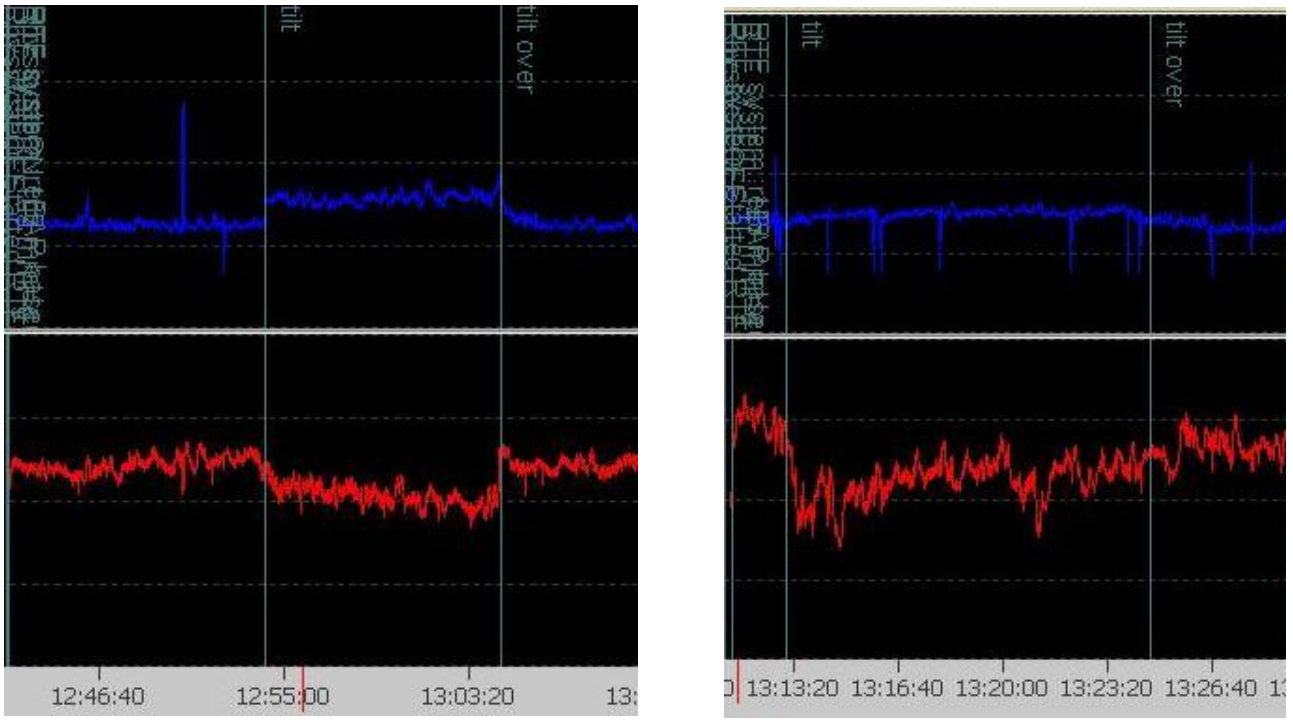


Figure 3: Blood pressure and heart rate changes with head up tilt test, this fig. showing drop in blood pressure more than 40 mmHg. Red colour indicate blood pressure and blue colour indicate pulse rate. X-axis indicate time and Y- axis indicate pulse rate and blood pressure

Heart rate variability with deep breathing was detected in 15 of 23 patients. It was mild in 8 of 23(34.8) patients and moderate in 7 of 23(30.4) patients. Valsalva ratio was abnormal in 15 of 23(65.2%) patients and it was mild.

Table 9: Heart rate variability with deep breathing and valsalva ratio in patients with CIDP

Heart rate variation with deep breathing	n/t (%)
Normal	8/23(34.8)
Decreased ≥ 50% of minimum	8/23(34.8)
Decreased ≤ 50 % of minimum	7/23(30.4)
Valsalva ratio, n/t (%)	
Normal	8/23(34.8)
Decreased ≥ 50% of minimum	15/23(65.2)
Decreased ≤ 50 % of minimum	0/23(0)

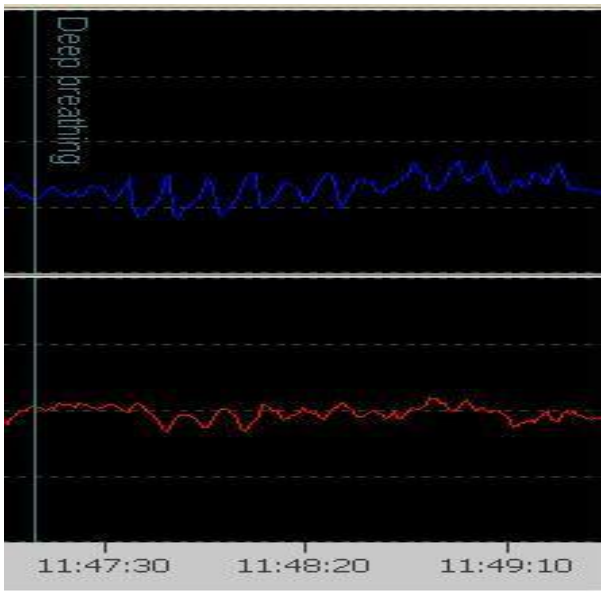


Figure 4 : Shows heart rate variation with deep breathing. Blue line indicates change in HR. Redline indicates changes in BP.

SSR was absent in 14 of 23 patients, It was absent in 12 of 23 in lower limbs and 2 0f 23 in both upper limbs and lower limbs.

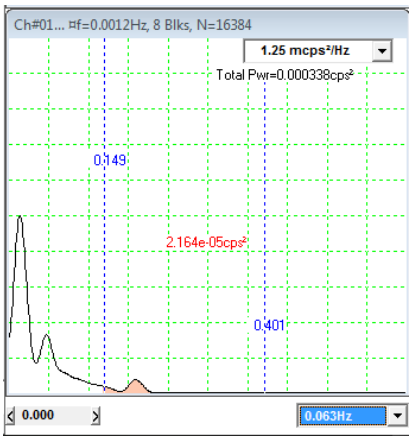
Table 10: SSR dysfunction in patients with CIDP

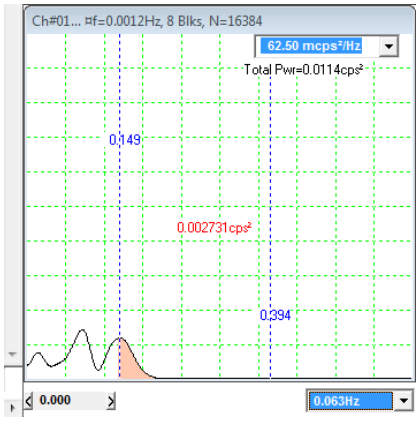
SSR	n/t (%)
Present in both upper limbs and lower limbs	9/23(39.2)
Absent in lower limbs	12/23(52.2)
Absent in both lower limbs and upper limbs	2/23(8.7)

Table 11: Comparison of Heart rate variability parameters (assessed by power spectral analysis) and Valsalva ratio, RSA

HRV variables	Study group(n=23) Mean ± SD	Control group(n=10) Mean ± SD	P value
HF nu at rest	23.84 ± 21.12	22.24 ± 26.26	0.652
LF nu at rest	53.49 ± 4.16	29.4 ± 26.57	0.02
HF nu at tilt	21.7 ± 21.7	17.5 ± 6.8	0.214
LF nu at tilt	39.4 ±19.38	49.8 ± 10.15	0.116
Valsalva Ratio	1.39±0.23	1.88±0.35	<0.001
RSA	10.40 ±7.89	19.29±5.58	0.004

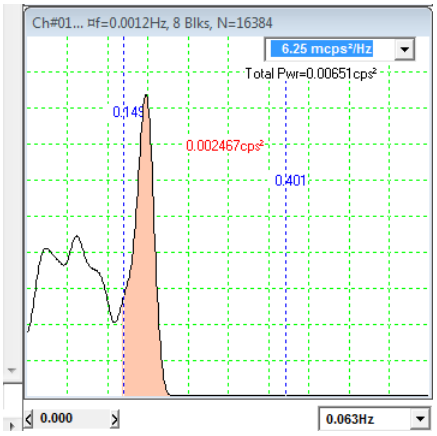
Fig: 5

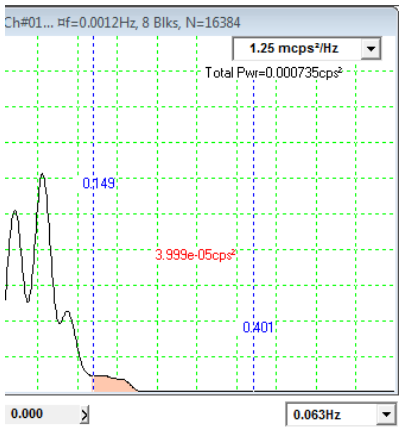




At Rest

Fig:6





At Tilt

Figure 5(Above): HF and LF changes at rest and at 70degree tilt position in healthy individual.

Figure 6(Below): HF and LF changes at rest and at 70degree tilt position in patient with CIDP with Sympathetic dysfunction. There was no increase in LF after tilting.

X-axis indicate frequency and Y- axis indicate power. HF from 0.15Hz to 0.4 and LF from 0.004 to o.15Hz

DISCUSSION

Majority of studies in literature are retrospective with paucity of prospective studies. There are no data from the India where the clinical profile and severity of illness might differ compared to the West. We studied the autonomic dysfunction in a prospective cohort of Indian patients with CIDP. The analysis included baseline demographic data, autonomic symptom profile, Total neuropathy score, quantitative autonomic function testing using tilt table test, heart rate variability analysis, sudomotor function testing using SSR.

This study reveals relatively high prevalence of autonomic symptoms and abnormalities in quantitative autonomic function tests in patients with CIDP. The prevalence of clinical symptoms of autonomic dysfunction in our study was about 60%. Stamboulis et al (n=17) reported autonomic symptoms in 64% of CIDP patients.(7) Figueroa et al (n=47) reported autonomic symptoms in 20-30% of CIDP patients.(4) Chiang et al. reported symptoms of autonomic dysfunction in 20% of CIDP patients (n=18).(50)The variation in frequency of symptoms between studies could be due to less emphasis on autonomic symptoms and due to recall bias in retrospective studies. This emphasizes the need for a systematic questionnaire based approach for exact documentation of the profile of autonomic symptoms such as COMPASS 31.

In this study we found that 19 of 23(82%) of CIDP patients had quantative autonomic dysfunction. In comparison, Stamboulis et al. (n=17) reported autonomic dysfunction in 76% of CIDP patients.(7) Figueroa et al (n=47) reported autonomic dysfunction in 47% of CIDP patients.(4)

The difference in prevalence of quantative autonomic dysfunction could be explained by study setting, methodology of autonomic function tests and temporal profile of disease.

Among 19/23 of our patients had abnormal autonomic function tests, among them 15/19 had clinical symptoms suggestive of autonomic system involvement. Stamboulis et al. reported (n=17) autonomic function tests abnormalities in 13 patients, among them 10 had clinical symptoms indicative of autonomic involvement. It was comparable our study.

In our study both parasympathetic and sympathetic systems were affected, cholinergic (70%) being more involved than adrenergic system (60%).Stamboulis et al. (n=17) reported both arms of autonomic systems were affected equally. Figueroa et al. (n=47) reported that cholinergic systems (40%) was involved predominantly with relative sparing of adrenergic system.

Lyu et al. reported autonomic dysfunction in CIDP patients (n=12), which involved both arms of autonomic system equally.(6)

In our study, the severity of autonomic dysfunction was assessed by using modified CAS scoring. In view of lack of facilities for QSART, SSR was used to assess sudomotor functions. It was incorporated in to CAS scoring and a modified CAS score was used for analysis. SSR was abnormal in 60% of our study population; it was comparable to 50 % (n=12) by Lyu et al study.

The mean CAS score of our study population was 3.26±1.91. In comparison, Figueroa et al reported mean CASS of 0.8±0.9 in patients with CIDP (n=47). Lyu et al. reported mean CASS of 2.7±2.0 in patients with CIDP (n=12). (6)(4)Our study population had a high modified CASS compared to other published studies, which has not been validated yet.

One important observation of our study was the high incidence of autonomic dysfunction. Majority of the patients were in clinical remission (complete/ partial) and were responders to the immunotherapy. The involvement of sympathetic and parasympathetic arms of the autonomic nervous system can be explained by involvement of small myelinated and unmyelinated nerve fibres, vagal nerve dysfunction with conduction blocks, secondary axonal loss. Involvement of the intermediolateral cell column in the spinal cord as a result of "bystander effect" and axonal degeneration has also been proposed.

Power spectrum analysis of heart rate variability was done by using Fourier analysis of regular beat-beat(R-R) intervals which were recorded for 5 min, converted in to a continuous function by linear interpolation and resample at 5Hz. In power spectrum, LF indicates predominantly sympathetic and HF indicates parasympathetic activity. Though we could not overall find any significant differences with frequency domain analysis using FFT, a few important observations were made.

In normal population, HF > LF during rest and LF > HF during standing/tilt. Tilting in normal individuals is usually associated with an increase in the low frequency components (sympathetic arm) with reciprocal decrease in high frequency component (parasympathetic dysfunction).

The CIDP patients in our cohort showed low LF power during the rest and the gain of LF during tilt was also suboptimal as compared to normal population indicating dysfunction of the sympathetic arm.

Power spectral analysis of heart rate variability has been studied in patients with Guillain–Barre´ syndrome to assess cardiovascular neural regulation showing that the sympathovagal balance is clearly shifted to sympathetic predominance at the height of the disease.(68) To our knowledge the same has not been studied in CIDP patients. Our study is the first to clearly document sympathetic dysfunction in CIDP cases using Power spectral analysis of Heart rate variability.

In our study autonomic deficits did not relate to somatic deficits, duration of disease, severity of disease and temporal profile of disease. Quantitative autonomic function deficits were also independent of autonomic symptom profile indicates subclinical autonomic dysfunction as previously reported by Stamboulis et al.

The autonomic dysfunction in our study was compared to autonomic dysfunction in amyloid neuropathy, small fiber neuropathy and other studies of CIDP with autonomic dysfunction as depicted in the table.

Patients with amyloid amyloid neuropathy,diabetic LRPN,autoimmune autonomic ganglinopathy had high CAS scores. Small fiber neuropathy and CIDP patients had mild to moderate CAS scores.50 % of patients with Small fiber neuropathy showed autonomic dysfunction. Whereas, studies with CIDP patients show variable involvement (from 50 to 75%).

Our study shows mild to moderate autonomic dysfunction documented with Modified CASS in at least 80% of cases.

Table 12: Comparison of CASS scores between our study with other studies (with CIDP and other neuropathies) reported in the literature.

CASS total and severity distribution

Neuropathic conditions	Mean	0%	Mild (1-3)	Moderate (4-6)	Severe (7-10)
CIDP (current study), mean (n - 23)	3.27	17	35	48	0
Cardiovascular autonomic function and SSR in CIDP by Lyu et al(n=12) (6)	2.7	25	50	25	0
Autonomic dysfunction in CIDP by Figueroa et al.(n=47) (4)	0.8	53	47	0	0
Amyloid neuropathy, (n - 58) (70)	6.7	0	10	42	48
Sicca complex-neuropathy, (n - 34)(71)	NA	15	38	35	12
Autoimmune autonomic ganglionopathy, (n -27)(72)	6.0	0	26	11	63
Small-fiber neuropathy,(n -125) (73)	2.7	48	24	27	1
Diabetic LRPN, (n - 14) (74)	7.0	0	29	14	57

The major strength of the study is the prospective nature with detailed symptom profile assessed by COMPASS 31 score and quantitative autonomic function testing. Our study is the first to assess HRV in CIDP using power spectral analysis. It appears that CIDP patients tend to have higher incidence of autonomic dysfunction than previously reported in literature. The dysfunction also is not restricted and appears to involve multiple domains of the autonomic nervous system.

Some of the limitations of the study include:

1. Small sample size
2. QSART was not done
3. Modified CASS was done using SSR has not been validated yet.
4. Patients are in remission at the time of testing

CONCLUSION

1.There is a high Prevalence of autonomic dysfunction is in patients with CIDP (80%).

2. The parasympathetic arm (70%)was more involved than sympathetic(60%).

4. Spectral analysis of HRV showing abnormality in sympathetic arm.

5.In our study 37 % had mild degree of autonomic dysfunction and 47% had moderate degree of autonomic dysfunction.

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ANNEXURES I

DATA COLLECTION PROFORMA

Autonomic dysfunction in CIDP

Name:	**Address:**
Hospital Number:	**Telephone/E-mail:**
DOB: **Age:**	**Seen by:**

History

Co-morbidities :

Hypertension Y / N Diabetes Y / N

General Examination:

Temp: Pulse: reg/irreg

Blood pressure: lying/ sitting/ standing/

Height: Weight: BMI :

Native medication Y / N Chronic liver disease Y / N

Neurological examination:

The Mini-Mental Status Examination (MMSE)	Points
Orientation Name: season/date/day/month/year Name: hospital/floor/town/state/country	 5 (1 for each name) 5 (1 for each name)
Registration Identify three objects by name and ask patient to repeat	 3 (1 for each object)
Attention and calculation Serial 7s; subtract from 100 (e.g., 93-86-79-72-65)	 5 (1 for each subtraction)
Recall [illegible]	3 (1 for each object)

Cranial Nerves

0 = Normal , 1 =Abnormal

Cranial nerves	
Olfactory	
Vision	
Fundus	
Eye movmnt	
Trigeminal	
Facial	
Vest Coclr	
Palate	
Sternomastoid	
Tongue	

Motor Examination

Bulk and Tone:

0 = Normal, 1 = Decreased , 3 Increased

Power

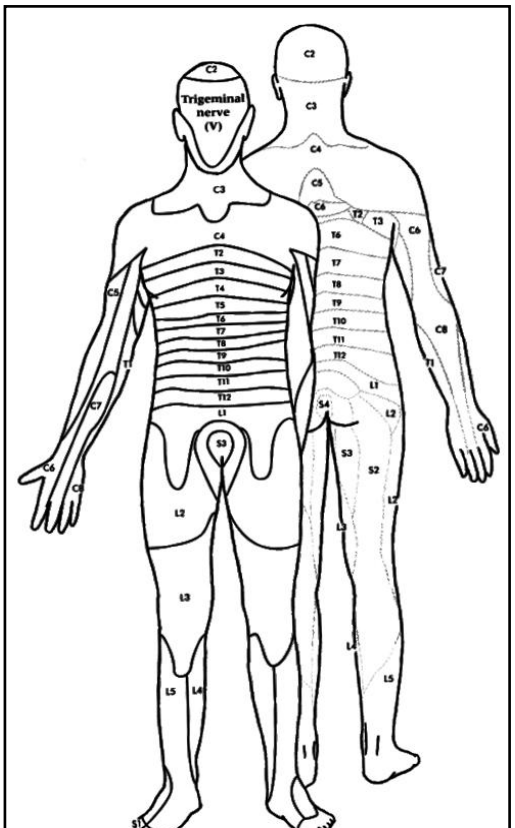
Power	R	L
Neck flx		
Neck ext		
Trunk		
Should Abd		
Should Add		
Elbow Flx		
Elbow Ext		
Wrist Flx		
Wrist Ext		

Reflexes

Reflexes	R	L
Biceps		
Brachiorad		
Triceps		
Knee		
Ankle		
Sup abd		

Sensory examination

	Sensory	R	L
Up.Limb	**Fine touch**		
	Vibration		
	Temperature		
	Joint pos		
	Monofilamnt		
Lo.Limb	**Fine touch**		
	Vibration		
	Temperature		
	Joint pos		
	Monofilamnt		



Cerebellar and Gait

Cerebel	
Romber	
Gait	
Nk stif	

0 = Normal, 1 = Abnormal

Electrophysiology

NCV	
EMG	

0 = Normal, 1 = Abnormal

Investigations

Hb	
TC	
DC	
Platelets	
Lipids	
AC	
PC	
Creat	

TOTAL NEUROPATHY SCORE

Parameter	Score				
	0	1	2	3	4
QST = quantitative sensory test; ULN = upper limit of normal; LLN = lower limit of normal.					

Parameter	Score				
	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Autonomic symptoms, n	0	1	2	3	4 or 5
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Vibration sensation (QST vibration)	Normal to 125% ULN	126 to 150% ULN	151 to 200% ULN	201 to 300% ULN	>300% ULN
Sural amplitude	Normal/reduced to <5% LLN	76 to 95% of LLN	51 to 75% of LLN	26 to 50% of LLN	0 to 25% of LLN
Peroneal amplitude	Normal/reduced to <5% LLN	76 to 95% of LLN	51 to 75% of LLN	26 to 50% of LLN	0 to 25% of LLN

COMPASS 31

1. In the past year, have you ever felt faint, dizzy, “goofy”, or had difficulty thinking soon after standing up from a sitting or lying position?
   1 Yes
   2 No (if you marked No, please skip to question 5)

2. When standing up, how frequently do you get these feelings or symptoms?
   1 Rarely
   2 Occasionally
   3 Frequently
   4 Almost Always

3. How would you rate the severity of these feelings or symptoms?
   1 Mild
   2 Moderate
   3 Severe

4. In the past year, have these feelings or symptoms that you have experienced:
   1 Gotten much worse
   2 Gotten somewhat worse
   3 Stayed about the same
   4 Gotten somewhat better
   5 Gotten much better
   6 Completely gone

5. In the past year, have you ever noticed color changes in your skin, such as red, white, or purple?
   1 Yes
   2 No (if you marked No, please skip to question 8)

6. What parts of your body are affected by these color changes? (Check all that apply)
   1 Hands
   2 Feet

7. Are these changes in your skin color:
   1 Getting much worse
   2 Getting somewhat worse
   3 Staying about the same
   4 Getting somewhat better
   5 Getting much better
   6 Completely gone

8. In the past 5 years, what changes, if any, have occurred in your general body sweating?
   1 I sweat much more than I used to
   2 I sweat somewhat more than I used to
   3 I haven't noticed any changes in my sweating
   4 I sweat somewhat less than I used to
   5 I sweat much less than I used to

9. Do your eyes feel excessively dry?
   1 Yes
   2 No

10. Does you mouth feel excessively dry?
   1 Yes
   2 No

11. For the symptom of dry eyes or dry mouth that you have had for the longest period of time, is this symptom:
   1 I have not had any of these symptoms
   2 Getting much worse
   3 Getting somewhat worse
   4 Staying about the same
   5 Getting somewhat better
   6 Getting much better
   7 Completely gone

12. In the past year, have you noticed any changes in how quickly you get full when eating a meal?
   1 I get full a lot more quickly now than I used to
   2 I get full more quickly now than I used to
   3 I haven't noticed any change
   4 I get full less quickly now than I used to
   5 I get full a lot less quickly now than I used to

13. In the past year, have you felt excessively full or persistently full (bloated feeling) after a meal?
   1 Never
   2 Sometimes
   3 A lot of the time

14. In the past year, have you vomited after a meal?
   1 Never

2 Sometimes
3 A lot of the time

15. In the past year, have you had a cramping or colicky abdominal pain?
1 Never
2 Sometimes
3 A lot of the time

16. In the past year, have you had any bouts of diarrhea?
1 Yes
2 No (if you marked No, please skip to question 20)

17. How frequently does this occur?
1 Rarely
2 Occasionally
3 Frequently _____ times per month
4 Constantly

18. How severe are these bouts of diarrhea?
1 Mild
2 Moderate
3 Severe

19. Are your bouts of diarrhea getting:
1 Much worse
2 Somewhat worse 3 Staying the same
4 Somewhat better 5 Much better
6 Completely gone

20. In the past year, have you been constipated?
1 Yes
2 No (if you marked No, please skip to question 24)

21. How frequently are you constipated?
1 Rarely
2 Occasionally
3 Frequently _____ times per month
4 Constantly

22. How severe are these episodes of constipation?
1 Mild

2 Moderate
3 Severe

23. Is your constipation getting:
1 Much worse
2 Somewhat worse 3 Staying the same
4 Somewhat better 5 Much better
6 Completely gone

24. In the past year, have you ever lost control of your bladder function?
1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

25. In the past year, have you had difficulty passing urine?
1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

26. In the past year, have you had trouble completely emptying your bladder?
1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

27. In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes?
1 Never (if you marked Never, please skip to question 29)
2 Occasionally
3 Frequently
4 Constantly

28. How severe is this sensitivity to bright light?
1 Mild
2 Moderate
3 Severe

29. In the past year, have you had trouble focusing your eyes?

1 Never (if you marked Never, please skip to question 31)
2 Occasionally
3 Frequently
4 Constantly

30. How severe is this focusing problem?
    1 Mild
    2 Moderate
    3 Severe
31. Is the most troublesome symptom with your eyes (i.e. sensitivity to bright light or trouble focusing) getting:
    1 I have not had any of these symptoms
    2 Much worse
    3 Somewhat worse
    4 Staying about the same
    5 Somewhat better
    6 Much better
    7 Completely gone

Composite autonomic scoring system

Index	Score	Parameter
Sudomotor index	**1**	Single site abnormal on quantitative sudomotor axon reflex test or length dependent pattern (distal sweat volume <1/3 of proximal site or persistent sweat activity at foot(On TST, anhidrosis present but<25%)
	2	Single site <50% of lower limit of QSART (On TST, anhidrosis 25-50%)
	3	Two or more sites < 50% of lower limit on QSART (On TST, anhidrosis >50%)
Adrenergic index	**1**	Early phase phase 2 decrease of <40 mmHg but >20 mmHg MAP or late phase 2 doses not return to baseline or decrease in pulse pressure to <50% of base line
	2	Early phase 2 decrease of <40 mmHg but >20 mmHg MAP + late phase 2 doses not return to baseline or decrease in pulse pressure to <50% of base line
	3	Early phase 2 decrease of > 40 mmHg + absent laste phase 2 and phase 4
	4	Criteria for 3+ orthostatic hypotension(systolic BP decrease of >30 mmHg: mean BP decrease of >20 mmHg)
Cardiovagal index	**1**	HR_{BD} or VR mildly decreased(above 50% of minimum)
	2	HR_{BD} or VR mildly decreased to 50% of minimum
	3	Both HR_{BD} and VR mildly decreased to 50% of minimum

Grading of autonomic failure

Composite autonomic scoring scale	Degree of autonomic failure
1-3	Mild
4-6	Moderate
7-10	Severe

EFNS/PNS 2010 criteria for diagnosis of CIDP:

Inclusion criteria

Patients diagnosed to have CIDP by EFNS/PNS 2010 criteria were included in the study. The criteria are mentioned below.

[A] Clinical criteria

[1] **Inclusion criteria**

(a) Typical CIDP

Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and

Absent or reduced tendon reflexes in all extremities

(b) Atypical CIDP (still considered CIDP but with different features)

One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):

Predominantly distal (distal acquired demyelinating symmetric, DADS) or

Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis–Sumner syndrome] or

Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)

Pure motor or Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)

[2] **Exclusion criteria**

Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy

Hereditary demyelinating neuropathy

Prominent sphincter disturbance

Diagnosis of multifocal motor neuropathy

IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein

Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexuneuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features

[B] Electro-diagnostic criteria:

(1) Definite: at least one of the following

(a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median at the wrist from carpal tunnel syndrome), or

(b) Reduction of motor conduction velocity ≤30% below LLN in two nerves, or

(c) Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN values), or

(d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1 other demyelinating parameters in ≥1 other nerve, or

(e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameters in ≥ 1 other nerve, or

(f) Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or

(g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve

(median≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibia ≥ l 8.8 ms) + ≥1 other demyelinating parameters in ≥1 other nerve

(2) Probable

≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak

CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parametera in ≥1 other nerve

(3) Possible

As in (1) but in only one nerve

[C] Supportive criteria:

1. Elevated CSF protein with leukocyte count <10/mm3

2 .MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses

3. Abnormal sensory electrophysiology in at least one nerve:

a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or

b. Conduction velocity <80% of lower limit of normal (<70% if SNAP amplitude <80% of lower limit of normal); or

c. Delayed somatosensory evoked potentials without central nervous system disease

4. Objective clinical improvement following immunomodulatory treatment

5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fiber analysis

Diagnostic categories

Definite CIDP

Clinical criteria 1 (a or b) and 2 with electrodiagnostic

Criterion 1; or

Probable CIDP + at least one supportive criterion; or

Possible CIDP + at least two supportive criteria

Probable CIDP

Clinical criteria 1 (a or b) and 2 with electrodiagnostic

Criterion 2; or

Possible CIDP + at least one supportive criterion

Possible CIDP

Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 3

CIDP (definite, probable, and possible) associated with concomitant diseases

AUTONOMIC FUNCTION TESTS

CARDIAC AND VASCULAR AUTONOMIC REGULATION TESTS:

1. Cardiovascular Responses to Standing and 30:15 ratio:

Studying blood pressure changes on standing is indicated in testing the integrity of the sympathetic adrenergic function. Studying heart rate changes to standing (30:15 ratio) is indicated in testing the integrity of parasympathetic cholinergic function. Measurements obtained after 20 min of supine rest. The blood pressure and heart rate are recorded at baseline and then serially for 1–3 min after postural standing. Orthostatic hypotension is present if there is a reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 min of standing. The 30:15 ratio, which is the ratio of the longest R-R (slowest heart rate) occurring about 30 beats after standing, divided by the shortest R-R (fastest heart rate), which occurs about 15 beats after standing .(50)(51) Normally the 30:15 ratio is greater than 1.04 and abnormal if less than 1.0. More precise age-related norms are: 10–29 years, >1.17; 30–49 years, >1.09; 50–65 years, >1.03.(52)

2. Head-Up Tilt-Table Testing:

Studying responses to tilt-table testing tests the integrity of the autonomic cardiovascular reflexes. The autonomic cardiovascular reflexes are similar but not identical to standing;

After connecting and ensuring proper placement of blood pressure sensor, baseline blood pressure will be measured for 5-10 minutes. Then patient will be tilted up to 70 degree smoothly

within 5-10 seconds (ensuring patient safety) .Then blood pressure will be measured every minute. During this period patient will be observed for the presence of any discomfort, chest pain, shortness of breath, dizziness, lightheadedness, and syncope. In case of any sign of an emerging adverse event, test will be terminated based on clinical judgment. Duration of the tilt will be at least 10 minutes and continued for 30 minutes if no obvious abnormalities are detected .On completion of test patient will be tilted back to baseline position. The positive response is syncope or pre syncope associated with a significant drop of blood pressure (usually greater than 20 mmHg systolic or 10 mmHg diastolic arterial pressure) or bradycardia. (53)

3. **Heart Rate Variation with Respiration (Sinus Arrhythmia):**

It tests the integrity of the parasympathetic cholinergic function. Inspiration increases heart rate, and expiration decreases it. The variation is primarily mediated by the vagus innervation of the heart. Sinus arrhythmia is influenced by several important factors. It decreases with age, CNS depressants, hyperventilation, cardiac failure and pulmonary diseases.The subject sits quietly and then breathes deeply at a rate of 6 breaths per minute. The ratio of the maximum – minimum heart rates to deep breathing is measured.

Normal values by age for 6 per minute deep breathing expressed as average (or mean) maximal-to-minimal variation in bpm are: 10–40 years, >18bpm; 41–50 years, >16 bpm;

51–60 years, >12 bpm; 61–70 years, >8 bpm.(54)(55)

4. **Valsalva maneuver and Valsalva Ratio:**

It tests the integrity of both sympathetic and parasympathetic nervous systems.

The blood pressure changes during maneuver tests the sympathetic adrenergic cardiovascular function and heart rate changes during maneuver tests the parasympathetic cholinergic function. Valsalva maneuver will be performed in supine position; the test will be started after patient is comfortable and relaxed. 2-3 practice sessions of Valsalva maneuver for short time will be given until patient is comfortable with the procedure. Patient is instructed to take a deep breath and blow into the syringe which is connected to a manometer. Patient is asked to maintain a pressure of 40 mm Hg for 15 seconds. If the pressure is suboptimal, patient will be instructed to correct the pressure or repeat the Valsalva maneuver. Same procedure repeated after 3 minutes, total 3 times and most appropriate maneuver will be selected for evaluation. The Valsalva maneuver has four phases as shown in the figure ….

The following parameters will be measured from the Valsalva maneuver test –

1. Valsalva ratio.
2. Maximal drop of the mean blood pressure during phase 2.
3. The peak of the mean blood pressure at the end of late phase 2 (recovery).
4. Overshoot, phase 4.
5. Maximal pulse pressure drop during phase 2

The Valsalva ratio is the ratio of the maximal heart rate in phase II to the minimal heart rate in phase IV. This may be calculated easily as the ratio of the longest R-R interval during phase IV to the shortest of phase II.

The Valsalva ratio of less than 1.2 as abnormal,1.2–1.45 as borderline, and greater than 1.45 as normal. Since the Valsalva ratio decreases with age, however, age specific norms are more

precise: 10–40 years,>1.5; 41–50 years, >1.45; 51–60 years, >1.45; 61–70 years, >1.35.(55)(54) The blood pressure drops of greater than 20 mmHg during early phase II in conjunction with either absent phase IV or absent late phase II are considered abnormal.

Miscellaneous Tests for cardiac and vascular autonomic functions:

1. **Blood pressure response to sustained hand grip:**

Sustained muscle contraction causes blood pressure and heart rate to increase.

The mechanism involves the exercise reflex, which withdraws parasympathetic activity and increases sympathetic activity.

The test requires the patient to apply and maintain grip at 30% maximal activity for 3 min. The diastolic blood pressure should rise more than 15 mmHg above base line; 11–15 mmHg rise is considered borderline. There is less experience with this test, and it has not been widely studied.(56)

2. **Blood pressure response to mental stress:**

Mental stresses such as arithmetic, sudden noise and emotional pressure cause sympathetic outflow to increase and with it blood pressure and heart rate. It has been used as a measure of sympathetic efferent function that has the advantage of not requiring direct afferent stimulation, but the test lacks sensitivity.(57)

3. **Cold pressor test:**

The patient submerges a hand in ice water, and subsequently there is a rise of blood pressure. The afferent limb of the reflex is somatic, and the efferent limb is sympathetic. The problems with the test are that it is difficult for many patients to maintain the hand in ice water for the requisite period of time, and the test lacks sensitivity, since many normal subjects do not have a significant rise of blood pressure.

4. **Plasma catecholamine levels and infusion tests:**

Normally upright posture induces vasopressor responses which are sympathetic and adrenergic, plasma norepinephrine levels nearly double.

In a preganglionic sympathetic disorder such as multisystem atrophy, resting supine norepinephrine levels are normal but fail to rise when standing because of the lack of preganglionic drive. In postganglionic sympathetic disorders such as progressive autonomic failure, resting supine norepinephrine levels are low and fail to rise when standing. Since metabolic clearance of norepinephrine varies, sensitivity of the test may improve using indices of norepinephrine biosynthesis. Various infusions such as norepinephrine, tyramine, isoproterenol, phenylephrine, edrophonium, Vasopressin, and angiotensin have been studied to evaluate autonomic responses, including afferent baroreflex sensitivity.

TESTS OF THERMOREGULATORY FUNCTION

1. **Sympathetic Skin Responses**:

The sympathetic skin response (SSR) test is a complex multi synaptic reflex with sudomotor

activity as final efferent arm. The SSR measures the evoked electro dermal activity. It is generated in sweat glands and surrounding dermis and epidermis in response to a stimulus. In a SSR, stimulation of somatic afferents results in activation of sympathetic, cholinergic, sudomotor post ganglionic axons which are the efferent components of somatosympathetic reflex response. The cerebral cortex, posterior hypothalamus, and ventro lateral brain stem reticular formation all affect the SSR.

Electro dermal activity is brought out either directly or reflexly. A direct response is recorded by stimulating a peripheral nerve or sympathetic trunk, which evokes a time-locked potential. Because of the difficulty in achieving the high threshold for activation of the un myelinated C fibers and the unavoidable simultaneous activation of pain fibers, direct responses are not studied in a clinical setting. A reflex is brought out indirectly by a wide variety of stimuli which activate the sympathetic nervous system and bring out the potential. The main advantages of the SSR are that it is sensitive, reproducible, semi quantitative, simple, fast, and readily obtained on most electro physiologic equipment.

The usual laboratory stimuli to elicit SSR are near noxious, electrical stimulation of sensory nerve preferably on a limb other than the one from which the response is recorded. Non noxious stimuli include mechanical, warm or cold thermal, startling auditory, emotional, deep inspiratory gasps, visual, mental stress etc. The SSR is usually recorded with standard surface electrodes with the active electrode on the palm of hand or plantar surface of foot, and a reference electrode on the dorsum of the same body part.

The morphology of the potentials recorded was diphasic with an initial negative peak followed by a larger positive peak, but the response may be monophasic, triphasic, or have an initial peak. Potentials are symmetric in homologous body regions. The potentials in the hands have larger

amplitudes and shorter latencies than those in the feet. The SSR is controlled by conduction along unmyelinated fibers, and latency measurement is not useful. Initially regarded as an all-or-none phenomenon, now as techniques are refined, amplitude criteria are defined. Amplitudes are difficult to define because of the variable morphology of the potential, but an increasing number of studies indicate usefulness of this parameter. According to Hoeldtke, latency in hands is 1.6 ± 0.1 s, amplitude in hands is 1.3 ± 0.2 mV, latency in feet is 2.1 ± 0.1 s, and amplitude in feet is 0.8 ± 0.1 mV. According to Knezevic, latency in hands is 1.5 ± 0.1 s, amplitude in hands is 0.5 ± 0.1 mV, latency in feet is 2.1 ± 0.2 s, and amplitude in feet 0.1 ± 0.04 mV. According to Drory, mean latency in hands is 1.5 s, mean amplitude in hands is 0.450 mV, mean latency in feet is 1.9 s, and mean amplitude in feet is 0.15 mV. (58)(59)(60) Patients with significant sensory neuropathy and reduced or absent somatic afferent input may not have electrically induced SSR, but may have EDA in response to some of the other stimuli noted above. This distinction could help differentiate sensory neuropathy with autonomic neuropathy from sensory neuropathy without autonomic involvement.

2. Quantitative sudomotor axon reflex test:

The QSART quantitatively assesses postganglionic sympathetic sudomotor axon and sweat gland function. QSART requires a multi compartmental sweat capsule and a sudometer.The different compartments of the sweat capsule allow for both stimulation and pickup of the sweating response. Stimulation requires a constant current generator which applies a current over one of the compartments to iontophorese acetylcholine onto the skin. The acetylcholine is iontophoresed at 2 mA for 5 min. Axon reflexes are generated when acetylcholine activates

nicotinic receptors in the sudomotor fiber terminal, sending impulses antidromically to branch points and then orthodromically back to remote neurosecretory synapses. In this way, the sudomotor axon is stimulated chemically, not electrically, by acetylcholine iontophoresis. Since this also stimulates sweat glands directly, the site of evaluation of the subsequent sweating responses is remote from the site of stimulation in a different compartment. Measurement requires a sudometer, which measures humidity. Low-humidity nitrogen gas is piped through the sudorometer to measure baseline or input humidity. The gas passes into the sweat compartment of the sweat capsule through an intake port and then exits the compartment through a different port. The gas passing over the skin is humidified by the sweat. It passes back to the sudorometer where the humidity is remeasured. The differences between the output and input humidities are recorded and quantified as a function of time. Recording continues for 5 min after cessation of the iontophoresis. The multi compartmental sweat cells are placed over four locations: the foot laterally in the distribution of the sural nerve, the distal leg proximal to the medial malleolus in the distribution of the saphenous nerve, the proximal leg just distal to the fibular head in the distribution of the peroneal nerve, and in the forearm medially in the distribution of the medial antebranchial nerve. QSART directly measures the activity of the postganglionic neurosecretory unit, allows delineation of proximal-to-distal topography, and provides a dynamic record of sudomotor function over time.

3. Thermoregulatory Sweat Test:

The TST is a sensitive test that provides quantative information on the distribution and pattern of sudomotor impairment.TST is dependent upon normal function of the pre ganglionic and post ganglionic components of sudomotor pathways.A powder contains alizarin red, which is orange

when dry but turns a deep purple color when sweating occurs, is applied to the forehead and the anterior surface of body. The patient is the put in a heated cabinet or heat cradle to provide a thermal stimulus that will increase the body temperature to 38° C or 1°C above the base line. An ambient temperature of 45° to 50° C, relative humidity of 30-40% and skin temperature of 39-40° C to cause generalized sweating with in 50 min in most normal subjects.The TST in combination with QSART helps to differentiate autonomic dysfunction is preganglionic or post ganglionic origin.

MISCELLANEOUS TESTS OF AUTONOMIC REGULATION:

1. **Tests of Exocrine and Pupillary Regulation:**

Sympathetic activity causes pupil dilation and contraction of Mueller's muscle in the upper lid. Parasympathetic activity causes pupil constriction, accommodation, lacrimation, and salivation. Pupillary function is often assessed by pharmacological testing. Pilocarpine and methacholine are parasympathomimetic agents which act directly on cholinergic parasympathetic constrictor muscles to cause pupillary constriction. In dilute amounts (pilocarpine 0.125% or methacholine 2.5% solution), they cause minimal constriction, but when there is parasympathetic denervation, there is denervation hypersensitivity, and the pupil constricts. Cocaine (4–5% solution) blocks reuptake of norepinephrine in sympathetic nerve terminals innervating papillary dilator muscles, and it causes pupillary dilation. In sympathetic denervation, norepinephrine is not present, and dilation does not occur when cocaine is applied.It helps in differentiating physiological anisocoria and sympathetic denervation. Hydroxyamphetamine is a sympathomimetic agent that releases norepinephrine; if the pupil fails to dilate when it is applied, the site of sympathetic denervation is postganglionic. Epinephrine acts directly on sympathetic adrenergic dilatory

muscles to cause pupillary dilation. In dilute amounts (0.1% solution), it normally causes minimal dilation, but when there is sympathetic denervation, there is denervation hypersensitivity, and the pupil dilates and it further confirms post ganglionic lesion. Lacrimation can be measured with the Schirmer's test. In the Schirmer's test, the wick end of a filter paper test strip is placed between the lower lid and the sclera. The length of wetting at 5 min is then measured,10 mm or more being normal. The sensitivity in detecting dry eyes is about 90%, and the specificity is about 85%. Salivation may be tested by having patients chew a series of five gauze pads for 1 min each for a total of 5 min after the sublingual gutter is wiped dry. Pretest weight is subtracted from posttest weight to calculate saliva production, normally greater than 7.5 mL/5 min.

2. Tests of Gastrointestinal Autonomic Regulation:

Videofluoroscopy and pharyngoesophageal motility studies help identify causes of dysphagia. GI motility, including gastric emptying times and colonic transit times, allows for identification of neurogenic disorders, but does not distinguish extrinsic autonomic disorders from intrinsic enteric nervous system disorders. Sympathetic denervation may be identified by various neurochemical studies including the norepinephrine and epinephrine responses to edrophonium, which rise promptly after intravenous administration when there is normal post ganglionic innervation. Parasympathetic denervation may be identified by the plasma pancreatic polypeptide response to sham feeding or hypoglycemia. Anorectal manometry helps identify causes of incontinence.

3. Tests of Genitourinary Autonomic Regulation:

Urodynamic studies in incontinent patients helps in identifying autonomic dysfunction.

Tests of male erectile function, such as nocturnal tumescence studies and penile rigidity studies, assess erectile function, which is largely controlled by vascular and autonomic function If abnormal, injection of vasoactive agents such as papaverine into the corpus cavernosum helps differentiate vascular from nonvascular dysfunction, poor response to injection means the cause is vascular.

Sno	Hospno	Name	Sex	Age	Onset	Duration	Course	Presentatic
1	384024F	Sanjay garc	1	49	42	7	2	0
2	521935c	Kasipandia	1	71	62	9	2	0
3	792294f	Kamal hald	1	34	32	2	1	0
4	266411f	Shajahan	1	53	51	2	2	1
5	802528f	Annamma	2	53	52	1	2	0
6	7772641f	Dipak mod	1	29	28	1	1	0
7	822957c	Ghan shyar	1	53	45	8	2	0
8	534698d	Sunil Pradh	1	43	39	4	2	1
9	769768f	Balasubran	1	63	59	4	2	1
10	113950f	Amit tiwari	1	29	27	2	1	0
70	817657f	Indra	2	61	60	1	1	0
12	811648f	Annapurna	2	56	53	3	1	0
13	793581f	Suresh pras	1	39	37	2	1	0
14	509670d	Abraham	1	43	39	4	1	0
15	708664f	Santhosh k	1	42	34	8	1	0
16	826855d	Mishri Pras	1	54	50	4	2	0
17	415991c	Ramjee mis	1	66	57	9	1	#NULL!
18	358713f	Ashok Pal	1	46	44	2	1	#NULL!
19	837687f	Sahad	1	33	32	1	1	#NULL!
20	901989F	Aditya kum	1	15	15	4	3	#NULL!
21	752331F	Prathap Ch	1	49	49	4	3	#NULL!
22	775677F	Hari Prasac	1	44	43	1	1	#NULL!
23	042661D	Nilratan	1	60	40	20	2	#NULL!
24			#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
25			#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
26			#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
27			#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
28			#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
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32			#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
33			#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
34			#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!

restothera	Ass	EFNSelectr	CSFcells	CSfprot	Biopsy	TNS	COMPASS3	OH
0	0	1	6	61	0	27	9	1
0	1	3	2	26	1	25	22	1
0	2	1	4	74	5	24	6	0
1	2	1	2	258	4	14	0	0
0	2	3	4	43	1	21	7	0
0	2	1	7	74	5	15	7	0
0	0	1	7	173	6	15	3	0
0	0	1	5	379	5	25	9	0
2	2	1	8	109	1	22	5	0
0	2	3	2	42	1	14	0	0
2	2	1	4	89	1	17	8	1
2	0	1	3	54	6	23	15	1
0	0	1	2	128	4	23	6	0
0	2	3	8	59	1	27	3	0
2	0	1	16	371	1	26	6	0
0	2	1	4	90	1	19	4	0
0	2	3	1	76	0	9	12	1
0	0	3	0	0	1	25	10	0
0	2	1	1	206	3	22	9	1
0	2	1	22	44	5	19	3	0
0	2	1	2	151	1	18	6	0
2	2	1	3	62	5	20	4	0
0	2	1	1	125	1	16	#NULL!	0
		#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
		#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
		#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
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Sudomotor	Vasomotor	GUsymp	Sexual	Gastro	Sicca	CAS	CASS	Cardiovaga
0	2	4	1	0	0	3	1	1
2	2	0	0	1	1	3	1	1
0	0	0	1	1	0	4	2	2
0	0	0	0	0	0	3	1	0
2	1	0	0	0	0	5	2	2
0	0	0	1	1	1	2	1	1
1	0	0	0	1	0	4	2	1
0	1	0	0	1	1	4	2	2
2	2	0	0	0	1	3	1	1
0	0	0	0	0	0	0	0	0
2	0	0	0	0	1	6	2	1
0	1	0	0	1	1	5	2	1
2	0	0	0	3	1	3	1	2
0	0	4	1	0	0	0	0	0
2	1	0	0	1	0	4	2	1
2	0	2	0	0	1	5	2	1
0	0	4	1	3	1	2	1	2
2	0	4	1	1	1	4	2	1
0	0	0	1	3	1	3	1	1
0	0	0	0	0	1	0	0	0
0	0	0	0	1	1	6	2	1
2	0	0	0	0	1	6	2	2
2	0	0	0	0	1	0	0	0
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
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Adrenergic	SSR	Blad	Tilt	Brea	Breath	Valasalv	Valsa	Mdr
1	1	#NULL!	0	8.16	1	1	1.18	13
1	1	#NULL!	0	1.83	2	1	1.07	0
1	1	#NULL!	0	3	2	1	1.34	0
2	1	#NULL!	0	10	0	0	1.36	21
3	0	#NULL!	1	4	2	1	1.21	11
0	1	#NULL!	0	11.6	1	0	1.59	10
3	0	#NULL!	1	15.8	0	1	1.32	17
2	0	#NULL!	0	4	2	1	1.22	17
2	0	#NULL!	0	4.6	1	0	1.6	26
0	0	#NULL!	0	22.5	0	0	1.64	14
4	1	#NULL!	1	5.83	1	1	1.27	49
3	1	#NULL!	1	35.16	0	1	1.36	16
0	1	#NULL!	0	2.83	2	1	1.15	0
0	0	#NULL!	0	11.4	0	0	1.52	0
2	1	#NULL!	0	9.5	1	0	1.57	34
3	1	#NULL!	0	13.33	0	1	1.3	42
0	1	#NULL!	0	2.6	2	1	1.28	0
0	2	#NULL!	0	18	0	1	1.1	0
2	0	#NULL!	0	10	1	1	1.26	12
0	0	#NULL!	0	18.2	0	0	2	14
4	1	#NULL!	1	9.3	1	0	1.55	32
1	2	#NULL!	0	3.5	2	0	1.47	0
0	0	#NULL!	0	14.1	0	0	1.8	0
#NULL!	#NULL!	#NULL!	#NULL!	32.8	#NULL!	#NULL!	2.4	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	23.3	#NULL!	#NULL!	1.7	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	16.5	#NULL!	#NULL!	1.7	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	17.8	#NULL!	#NULL!	1.6	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	16.3	#NULL!	#NULL!	1.75	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	17.83	#NULL!	#NULL!	1.52	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	18	#NULL!	#NULL!	1.5	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	15	#NULL!	#NULL!	2.4	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	16.1	#NULL!	#NULL!	2.1	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	15.8	#NULL!	#NULL!	2.2	#NULL!
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Maxbp	recovery	over	Systolic	Diastolic	Mean	Systolic30	Diastolic30	Mean30
0	0	1	130	75	97	115	75	90
0	1	1	172	76	110	143	61	89
0	1	1	133	81	104	141	96	115
1	0	1	150	86	109	128	78	95
0	0	0	140	82	103	120	81	97
0	1	1	118	74	93	105	70	85
0	0	0	151	99	118	124	78	97
0	1	0	113	74	95	126	81	101
1	0	1	104	76	86	75	61	67
0	1	1	128	76	94	121	76	93
2	0	0	168	76	108	112	62	77
0	0	1	160	83	112	146	95	116
0	1	1	151	104	120	120	101	99
0	1	1	130	80	100	103	100	97
1	0	0	170	100	130	160	109	125
2	0	0	140	81	106	141	78	103
0	1	1	139	82	108	111	78	94
0	1	1	107	56	77	95	59	74
0	1	1	139	70	98	124	71	91
0	1	1	117	81	101	116	83	98
1	0	0	154	84	114	99	54	67
0	0	1	148	67	93	142	72	94
0	1	1	138	67	89	116	65	82
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
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Systolic1	Diastolic1	Mean1	Systolic3	Diastolic3	Mean3	Systolic5	Diastolic5	Mean5
128	84	98	128	79	95	126	77	93
152	65	94	153	63	93	155	66	95
149	96	122	143	90	107	146	90	108
138	76	96	150	87	108	144	75	98
92	65	74	98	69	78	111	71	84
111	78	89	121	79	93	124	84	97
108	74	82	100	69	79	97	70	79
131	85	100	121	80	93	122	81	94
86	65	72	106	78	87	101	74	83
128	81	96	122	77	92	124	84	103
113	49	70	123	54	77	121	46	71
136	61	84	130	73	92	145	74	97
137	82	100	145	89	107	150	91	110
122	77	92	121	81	94	116	78	89
174	118	136	179	120	139	158	103	121
138	74	95	138	76	96	128	75	92
115	80	91	121	81	94	116	73	87
100	61	74	100	60	73	104	60	74
119	65	83	122	74	90	121	77	91
114	82	96	118	85	104	112	82	98
106	54	73	106	53	72	135	80	103
148	75	96	156	78	102	141	73	95
120	67	85	128	67	90	120	66	85
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Systolic10	Diastolic10	Mean10	HR	HR30	HR1	HR3	HR5	HR10
128	80	96	92	100	105	97	93	94
164	71	102	74	73	74	72	73	73
138	90	166	79	85	81	81	84	82
164	82	110	65	89	40	88	88	81
129	79	92	69	85	79	96	78	67
107	67	80	90	93	98	98	102	107
138	83	107	91	89	96	92	95	86
124	81	98	94	103	103	98	98	99
90	70	78	85	87	88	92	88	91
131	85	100	86	94	96	90	98	100
157	70	100	82	90	89	90	90	88
146	82	108	104	82	108	107	113	81
139	89	105	108	120	105	106	109	112
118	81	93	98	65	102	101	105	100
170	108	129	84	88	88	90	72	80
131	74	93	76	77	71	70	75	65
127	80	95	76	79	81	79	77	79
108	63	78	64	70	71	72	75	75
118	76	90	71	85	81	82	85	88
109	81	92	67	71	65	73	73	87
125	69	92	63	67	75	73	73	87
143	73	96	83	92	94	47	94	105
121	68	89	63	67	75	73	75	75
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
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Hypert	Diabet	CAD	Toxin	CTDs	Chronic	Malignancy	Paraprotei	FamilHis
0	0	0	0	0	0	0	1	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	1	0
0	0	1	0	0	0	0	1	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	1	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	1	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	1	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
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Sensory	Weak	typical	Cardio	Adre	Sudo	totalR	HFR	LFR
2	1	1	1	1	1	0.000735	4E-05	0.000483
2	1	1	2	0	1	0.00922	0.003705	0.004878
2	1	1	2	1	1	1.09E-05	1.09E-05	5.22E-08
2	1	2	0	2	1	0.0422	0.01819	0.02061
2	1	1	2	3	0	0.000102	3.35E-05	6.08E-05
2	1	1	1	0	1	0.00434	0.001078	0.002759
2	1	1	1	3	0	0.00146	3.81E-05	0.000429
2	1	1	2	2	0	0.0148	1.15E-07	5.17E-07
2	2	2	1	2	0	0.0015	0.000273	0.000709
2	2	2	0	0	0	0.000333	2.04E-05	0.000185
2	1	1	1	4	1	0.00621	0.002152	0.003595
2	1	1	1	3	1	0.00471	0.001472	0.002011
2	1	1	2	0	1	0.00095	0.000221	0.000554
2	1	1	0	0	0	0.024	0.003862	0.01601
2	1	1	1	2	1	0.000712	8.06E-05	0.000408
2	1	1	1	4	1	0.00176	0.000501	0.000806
2	1	1	2	0	0	4.84E-05	3.74E-06	1.77E-05
2	1	1	1	0	3	0.000264	9.52E-06	0.000103
2	1	1	1	2	0	0.000912	0.000108	0.000632
2	1	1	0	0	0	0.0094	0.002457	0.005287
2	1	1	1	4	1	0.0122	0.002033	0.007922
2	2	2	2	1	0	0.0284	0.0048	0.0137
2	1	1	0	0	0	0.0165	0.002981	0.01037
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	0.0282	0.0046	0.0136
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	0.000484	0.5037	0.00176
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	0.00333	2.04E-05	0.000185
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	0.0231	0.003352	0.01645
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	0.00138	0.000194	0.000669
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	0.0388	0.00412	0.2741
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	0.00651	0.002467	0.003075
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	0.00129	0.000227	0.000592
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	0.015	0.01366	0.01036
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	0.138	0.002376	0.009432
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!

TotalT	HFT	LFT	HFnu	LFNUrest	patcontrol	HFnutilt	lfNUTILT
0.000338	2.16E-05	0.000117	0.0544	0.657	1	0.064	0.346
1.09E-05	1.08E-05	0	0.402	0.529	1	0.995	#NULL!
0.000598	0.000226	1.24E-05	0.996	#NULL!	1	0.378	0.0207
0.0452	0.02799	0.009323	0.431	0.488	1	0.619	0.206
0.000359	0.000101	0.000215	0.328	0.596	1	0.282	0.599
0.00891	4.81E-08	2.09E-07	0.248	0.636	1	#NULL!	#NULL!
0.0011	0.000242	0.000638	0.0261	0.294	1	0.22	0.58
0.000269	2.65E-05	0.000103	#NULL!	#NULL!	1	0.0986	0.384
0.00429	0.000949	0.002398	0.182	0.473	1	0.221	0.559
0.000313	2.37E-05	0.000118	0.0613	0.556	1	0.0758	0.377
0.000482	0.000127	0.000185	0.347	0.579	1	0.264	0.384
0.00173	0.000391	0.01083	0.313	0.427	1	0.226	#NULL!
0.00466	0.000855	0.002744	0.232	0.583	1	0.183	0.589
0.00503	0.001186	0.002806	0.161	0.667	1	0.236	0.558
0.00119	9.81E-05	0.000676	0.113	0.573	1	0.0824	0.568
0.000759	7.34E-05	0.000429	0.285	0.458	1	0.0967	0.565
0.00323	0.00079	0.002	0.0772	0.365	1	0.245	0.619
0.000319	8.93E-06	0.000103	0.036	0.392	1	0.028	0.322
0.000843	4.81E-05	0.000525	0.118	0.693	1	0.0571	0.623
0.00255	0.000215	0.001638	0.261	0.562	1	0.0842	0.642
0.00242	0.000557	0.01399	0.167	0.649	1	0.23	#NULL!
0.0255	0.005589	0.01418	0.169	0.482	1	0.219	0.556
0.000589	4.9E-05	0.000327	0.181	0.628	1	0.0832	0.555
0.0254	0.005587	0.01417	0.1631	0.482	2	0.22	0.558
0.00323	0.00079	0.002	#NULL!	#NULL!	2	0.245	0.619
0.000313	2.37E-05	0.000118	0.0061	0.0556	2	0.0757	0.377
0.000141	1.81E-05	6.31E-05	0.1451	0.712	2	0.128	0.448
0.0017	0.000154	0.01167	0.1405	0.485	2	0.0908	#NULL!
0.00139	0.000363	0.000932	0.1062	#NULL!	2	0.261	0.671
0.0114	0.002731	0.00703	0.379	0.472	2	0.24	0.617
0.0068	0.001029	0.004038	0.1758	0.459	2	0.151	0.594
0.00996	0.00212	0.00635	0.9107	0.691	2	0.213	0.638
0.00513	0.000633	0.002337	0.0172	0.0683	2	0.123	0.456
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!